Von Hippel-Lindau Syndrome

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Glossary

allele Alternative forms of a gene at a given location.

mosaicism A condition in which an individual or tissue has two or more cell lines differing in genotype or karyotype, derived from a single zygote.

penetrance The percentage frequency with which a heterozygous dominant, or homozygous recessive, mutant gene produces the mutant phenotype (observable expression). Failure to do so is (loosely) called "nonpenetrance" and penetrance of less than 100% is "reduced penetrance."

phenocopy A phenotype produced by environmental factors that mimics a genetically determined trait when there is no change in the corresponding gene.

phenotype The observed result of the interaction of the genotype with environmental factors; the observable expression (characteristics of an individual) of a particular gene or genes.

tumor suppressor gene A normal gene involved in the regulation of cell growth. Tumor development can result from recessive mutations, such as in the retinoblastoma or p53 genes.

Von Hippel-Lindau syndrome (VHL) is an autosomal-dominant heritable neoplastic disorder in which multiple benign and malignant neoplasms and cysts of specific histopathologies develop in the kidney, adrenal gland, pancreas, brain, spinal cord, eye, inner ear, epididymis, and broad ligament, associated with germ-line mutations in the VHL tumor suppressor gene at chromosome 3p25–p26.

INTRODUCTION

The most well-studied form of familial clear cell renal cell carcinoma (RCC) is von Hippel-Lindau syndrome (OMIM 193300), an autosomal, dominantly inherited multisystem neoplastic syndrome. It predisposes to renal cancers and cysts, pheochromocytoma, pancreatic neuroendocrine tumors (PNETs), central nervous system (CNS) hemangioblastoma, retinal angioma, endolymphatic sac tumor (ELST), and papillary cystadenoma of the epididymis and broad ligament. It is common for some affected individuals to develop multiple and/or bilateral tumors in most or all of the target organs of VHL. The prevalence of VHL has been estimated at between 1 per 35,000 and 1 per 40,000 by Neumann and Wiestler, and by Maher and colleagues.

Historically, the median age at death has been estimated at 49 years, but this may no longer be correct since extensive screening and treatment approaches have been adopted. Death most commonly is caused

by neurologic complications of brain hemangioblastomas or by metastatic renal cell cancer.

Significant advances have been made in the understanding of the VHL gene and its pathway. These advances have led to improvements in genetic diagnostics, the availability of presymptomatic screening, and new treatment methods, including organ-sparing surgeries, with the intent of increasing the quality of life and life-span of affected individuals.

History

More than 100 years ago, incomplete clinical descriptions of the disorder of what has come to be known as VHL were first reported. Illustrations of angiomas of the eye and similar vascular lesions of the cerebellum began appearing in reports as early as the 1860s. By 1904, Eugen von Hippel (1867–1938), a German ophthalmologist, published descriptions of retinal angiomas in several generations of family members in a small number of kindreds. In 1926, Arvid Lindau (1892–1958), a Swedish pathologist in Lund, published his thesis recognizing that retinal angiomas and cerebellar hemangioblastomas as well as cysts in the kidney, pancreas, and epididymis were part of a familial syndrome. Among the subsequent reports that refined the clinical understanding of VHL, Melmon and Rosen's landmark summary in 1964 established the first diagnostic criteria and included renal cancer. Linkage of the VHL gene to the short arm of chromosome 3 was reported by Seizinger and colleagues in 1988. Finally, in 1993, Latif and colleagues identified the VHL tumor suppressor gene by positional cloning strategies.

GENETICS

Molecular Genetics

The VHL gene is located at chromosome 3p25-p26 and is a tumor suppressor gene. This gene is also conserved in many species, including insects through mammals, and thus its functions are considered to be fundamental to life. Mutations causing loss or inactivation of the wild-type allele from the unaffected parent are thought to transform a cell into the clonal progenitor of a tumor.

Mutations causing VHL have been detected in all three exons and some intronic regions of the VHL gene. Mutation types identified include missense mutations, nonsense mutations, and partial and complete deletions of the gene. In 1996, Zbar and international collaborators reported more than 137 different *VHL* mutations identified from patients in North America, Europe, and Japan. It is possible that exon 2 of the VHL gene may have a specific role in RCC development, as 45% of patients with mutations in exon 2 have RCC.

VHL Complex

The VHL gene product (pVHL) binds with elongin C, which binds elongin B, Cul2, and RBX1 to form a multimeric complex. The VHL complex targets the hypoxia-inducible factors (HIF) HIF1-α and HIF2-α for ubiquitin-mediated degradation. Under normoxic conditions, the complex degrades HIF. Under hypoxic conditions, HIF is not degraded and it overaccumulates. Increased levels of HIF are associated with increased transcription of a number of downstream genes, including vascular endothelial growth factor (VEGF), erythropoietin, platelet-derived growth factor, Glut1, and transforming growth factor-α. Mutations of the VHL gene in the α-domain (elongin C binding) or the β-domain (HIF targeting) have been shown to be associated with increased HIF levels. VEGF is a known promoter of tumor angiogenesis, which may account for the vascular nature of VHL tumors.

Genetic Counseling, Family Screening, and Molecular Diagnosis

VHL is transmitted in an autosomal-dominant pattern of inheritance with reproductive consequences. Each offspring of an affected parent has a 50% chance of inheriting the mutated copy of the VHL gene, putting them at risk for VHL tumors and for transmitting the trait. Offspring who inherit the affected parent's wild-type allele are not at risk for VHL and cannot transmit the trait for VHL.

Detection of the *VHL* mutation was possible in 93 of 93 VHL families, as reported by Stolle and colleagues in 1998. Laboratories utilize multiple molecular techniques, including DNA sequencing, for the detection of *VHL* point mutations. Gene deletions may be detected by quantitative Southern blotting and, in some instances, fluorescence *in situ* hybridization is available for *VHL* mutation analysis in a growing number of Clinical Laboratory Improvement Amendment (CLIA)-certified clinical laboratories.

Genetic testing should occur within the context of genetic counseling as recommended by the American Society of Human Genetics, the American Society of Clinical Oncologists, and other medical societies. Before being tested, patients make the decision to be

Table I Approach to Diagnosis of von Hippel-Lindau Syndrome Assisted by DNA Testing

Obtain a geneticist, genetic counselor, and/or physician to assist:

(1) Clinically document von Hippel-Lindau syndrome (VHL) in a family member.

(2) Analyze the member's peripheral blood lymphocyte DNA for a mutation in the VHL gene.

(3) If a mutation is identified,[a] the DNA-tested family member's first-degree relatives who wish are counseled, sign informed consent, and have their blood cells' DNA tested for the same mutation. All those found positive for the VHL gene mutation, then have DNA testing offered to their remaining first-degree relatives.

(4) Clinical screening is offered to all those found to carry the VHL gene mutation.

Note. VHL penetrance has been estimated at > 90%.

[a]*De novo* VHL in sporadic cases may have clinical manifestations, but patients may not have a mutation identified in their peripheral blood leukocyte DNA. The offspring of patients are considered to be at risk unless they are shown to have a normal VHL gene.

tested, after discussing the medical and psychosocial implications for themselves and their families. Post-test genetic counseling continues through disclosure of genetic results.

Discovery of a germ-line genetic mutation is an indication for a lifetime of periodic screening for VHL tumors and cysts. Early detection and management of VHL-related tumors may result in decreased morbidity and mortality and improved quality of life. At-risk biological relatives need genetic counseling, clinical screening, and/or genetic testing to clarify VHL risk. Presymptomatic detection of this highly treatable disease is aided by genetic diagnostic testing (see Table I). The choice to be tested must be entirely voluntary after informed consent is given and a consent document is then signed.

De novo mutations present a special challenge in genetic counseling and genetic diagnostic testing. The frequency of new germ-line mutations in *VHL* is not known. Sgambati and co-workers in 2000 reported that in a registry of 181 kindreds, 42 (23%) included a first in family diagnosis. When 2 (4.8%) of the 42 were further analyzed by additional molecular investigations, VHL mosaicism was demonstrated. New mutations may arise as any one of three types of sporadic VHL mosaicism, depending on which tissues have cells with a *VHL* mutation. Mosaicism is present in varying degrees and may include VHL gene mutations in somatic tissue only, in somatic plus germ tissue (spermatocyte, oocyte), or in germ tissue only.

CLINICAL MANIFESTATIONS

Common manifestations of VHL are renal cell carcinoma and cysts, pheochromocytoma, pancreatic neuroendocrine tumors, benign cysts of the pancreas, hemangioblastomas of cerebellum or spinal cord and medulla, retinal angiomas, endolymphatic sac tumor, and papillary cystadenomas of the epididymis and broad ligament.

The VHL clinical phenotypic expression is variable among families, which is thought to be mainly attributable to genotypic differences. Variability within families is also seen with regard to age of onset and severity of disease. In the latter case, other influencing factors, including modifier genes and lifestyle choices, such as cigarette smoking, are being studied. Classification of VHL into phenotypic subtypes has been correlated with genotypes to the extent possible (Table II). Type I, type IIA, and type IIB were initially described, and type IIC has been described in a number of reports and was the focus of the report from the laboratory of Kaelin and colleagues in 2001.

Age of onset of VHL is variable, with a mean age of onset of 25, 30, and 37 years for patients with tumors of the eye, CNS, and kidney, respectively. However, there are reports of children with retinal angioma at 1 year of age, with CNS hemangioblastoma at 11 years of age, and clear cell RCC at 16 years of age. Pheochromocytomas can occur in children as young as 6 years of age. In contrast, VHL expression can be very delayed; the diagnosis can occasionally be delayed until the eighth decade, supporting the need for lifelong monitoring of individuals at risk.

Table II Von Hippel-Lindau Syndrome (VHL) Classification

I. VHL *without* pheochromocytomas

II. VHL *with* pheochromocytomas

- A. Pheochromocytomas, retinal angiomas, and CNS hemangioblastomas
- B. Pheochromocytomas, retinal angiomas, CNS hemangioblastomas, clear cell RCC, and pancreatic neoplasms and cysts
- C. Pheochromocytomas only

Note: VHL type I and type IIB differ only by the absence (I) or presence (IIB) of pheochromocytoma. Endolymphatic sac tumors and cystadenomas of the epididymis and broad ligament have not been assigned to specific VHL types.

Table III Screening[a] Guidelines for Von Hippel-Lindau Syndrome (VHL)

Test	Age
Ophthalmoscopy yearly	From infancy
Fluorescein angioscopy	As needed
Urinary catecholamines	From age 2 years, every 1–2 years
Enhanced MRI, brain/spine	From age 11 years, every 2 years;[b] after age 60 years, every 3 years
Abdominal CT w/ and w/o contrast	From age 18 years, every 2 years
Abdominal US	Yearly from age 11 to 18 years when abdominal CT begins
Neurotology examination	Any age if there is hearing loss, tinnitus, or vertigo

[a]Screening tests of specific organ sites are modified and may be increased in frequency at sites where VHL tumors or cysts are detected.
[b]Examine area of internal auditory canals for signs of endolymphatic sac tumor.

When clinical evidence of VHL is unclear, genetic testing (in all but some mosaic cases) should detect a mutation in the VHL gene when there is a risk for VHL. Identified risk indicates a need for age-appropriate baseline clinical screening and a lifetime of periodic monitoring (Table III), as well as a 50% chance for each offspring to inherit the trait and carry the risk for VHL.

Treatment of any one VHL manifestation must be prioritized along with knowledge of the other VHL tumors and cysts present in the patient. In particular, pheochromocytoma must be ruled out before any surgery. In the case of abdominal surgery, preoperatively, one must also consult the neurosurgeons to evaluate for unstable CNS masses.

Clear Cell Renal Cell Carcinoma: Solid and Cystic Disease

Renal cell carcinoma is detected in approximately 24–45% of individuals with VHL disease. Males and females are affected approximately equally, unlike sporadic RCC, which occurs more often in males.

Multiple bilateral VHL clear cell renal lesions develop, within which a few have scattered granular cells. These tumors tend to be low grade and minimally invasive when they are small and become more aggressive as they enlarge. Only 1 of 66 malignant lesions examined by Poston and colleagues in 1995 was found to have sarcomatoid renal cell carcinoma with clear and granular cells. Although microscopic invasion of the pseudo-capsule was common (52%), no tumor extension through the pseudo-capsule was identified in a study of 161 renal lesions. There is wide variation in the growth rate of solid tumors in VHL, which Choyke and colleagues in 1992 have shown to be 0.2–2.2 cm/year (mean 1.6 cm/year). There is a single case report of metastatic disease occurring in VHL with a primary renal tumor less than 3 cm in diameter.

As many as 63% of people with VHL have renal cysts. Complex renal cysts in VHL disease have been shown to harbor clear cell RCC in many cases. Although renal cystic disease in VHL may have the appearance of polycystic kidney disease, in VHL, periodic monitoring of renal cystic disease is recommended, as malignancy may be present.

A high prevalence of microscopic lesions in grossly normal renal parenchyma was identified and reported by Walther and colleagues in 1995. Based on extrapolations from grossly normal renal parenchyma removed at the time of partial nephrectomy, up to an estimated 600 microscopic "tumorlets" and 1100 microscopic cysts with clear cell lining may be present in the kidney of a 37-year-old with VHL. In the follow-up study reported in 1996 by Lubensky and colleagues, allelic deletion of the VHL gene was present in microscopic clear cell renal lesions. They identified loss of the wild-type VHL allele and retention of the inherited mutated VHL allele early in the development of renal clear cell lesions.

Diagnosis

Primary kidney tumors may grow for many years before symptoms manifest. In a screened population, renal tumors are often diagnosed incidentally during imaging studies for another purpose. The classic triad of pain, palpable mass, and hematuria is very rare and when seen is often associated with large renal masses. Presymptomatic screening protocols (Table II) for individuals at risk for VHL are recommended to identify tumors at a stage when they may be managed with good outcome.

Computed tomography (CT) remains the gold standard for diagnosis of renal involvement in VHL. Contrast-enhanced CT in thin sections of 3–5 mm before and after intravenous non-ionic iodinated

contrast medium is essential for best detection and spiral geometry may decrease the chances of missing lesions (Fig. 1). Ultrasound is less sensitive than CT and is not considered reliable for lesions smaller than 2 cm. However, ultrasound is often useful in determining whether a lesion is cystic or solid. Magnetic resonance imaging (MRI) may be used in cases in which CT is contraindicated, for example, when there is impaired renal function. Patients with VHL commonly have normal renal function even when there are multiple tumors and cysts in their kidneys. Renal lesions in patients with VHL are most often considered suspicious for cancer and it is recommended that they be followed if they are not yet large enough to warrant immediate treatment.

Treatment

Nephron-sparing surgery was designed to minimize the risk of metastasis yet preserve kidney function. Walther and colleagues reported in 1999 their 10-year experience with preserving kidney function by using a 3 cm threshold for renal parenchymal-sparing surgery. In 52 patients with VHL who had partial nephrectomies and a median follow-up of 60 months (ranging from 6 to 205 months), there were no metastases and none of these patients needed dialysis or transplantation.

Each patient's treatment may be tailored according to the location and sizes of renal masses on imaging studies. Preoperative evaluation in VHL includes evaluations for pheochromocytoma and hemangioblastomas of the central nervous systems as both lesions in these locations have the potential to cause significant adverse consequences in the operative and perioperative period if undetected.

Radiofrequency ablation, a newer treatment modality, is being evaluated in VHL patients as an alternative to surgery. Early results are encouraging for this method of tumor ablation, which may have significantly reduced morbidity compared to surgery. However, it is too early to determine the role of this method of treatment for patients with VHL-associated renal cell carcinoma.

Kidney transplantation after bilateral nephrectomy is performed when the option of nephron-sparing surgery is no longer viable. In addition to the usual protocol rules guiding organ transplantation for individuals who have had cancer, the hereditary nature of VHL adds another dimension in selecting a living related donor. It is recommended that potential related donors be screened with genetic testing. Furthermore, the long-term effects of immunosuppression in VHL with regard to tumor development are incompletely understood.

Sporadic Clear Cell Renal Carcinoma and VHL Gene Mutations

Approximately 60% of tumors from patients with sporadic clear cell renal cancers unrelated to VHL have been found to have mutations in the VHL gene. Somatic mutations in both alleles of the VHL

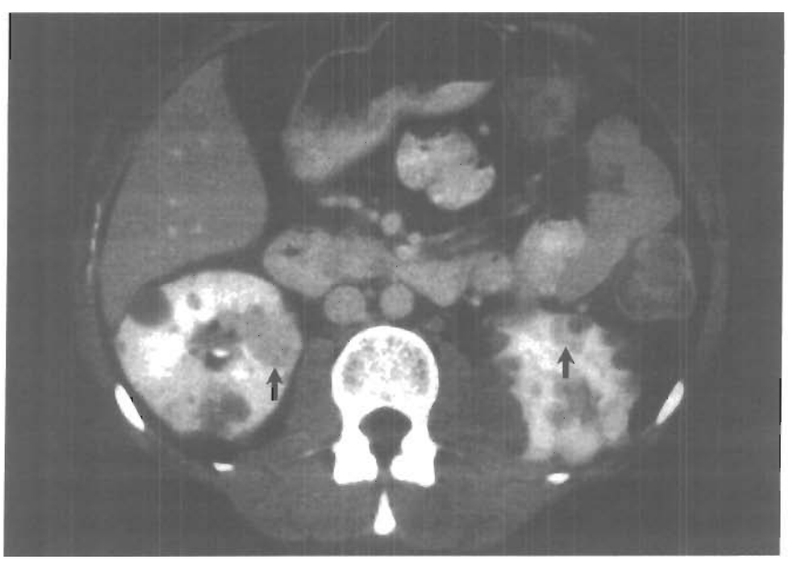

Figure 1 A CT scan of a 44-year-old female with VHL and severe renal manifestations, including bilateral renal cell carcinomas (arrows) and numerous bilateral renal cysts.

gene have been shown in many clear cell RCCs. This is strong evidence supporting the VHL gene as being important in the development of clear cell carcinoma of the kidney.

Phenocopies

In kindreds with VHL, sporadic clear cell RCC may arise even in the absence of the VHL gene mutation. This has been observed in individuals from two kindreds. One family member with clear cell RCC who was a heavy cigarette smoker was shown to be negative for the VHL germ-line mutation present in her relatives with VHL. These phenocopies apparently represent sporadic cases of renal cancer occurring in families with VHL.

Risk Factors in RCC

Environmental factors, as well as heritable genetic factors, have been shown to be associated with mutations in the VHL gene. It has been widely reported that cigarette smoking may be a risk factor for the development of kidney cancer. In addition, in 1999, Brauch and colleagues reported high cumulative trichloroethylene (TRI) exposure in workers who later developed RCC with a unique mutation pattern found in the VHL gene. In the past, TRI was used in industrial solvents.

Pheochromocytoma

The exclusion of pheochromocytoma prior to any surgery and before the onset of labor and delivery can be a life-saving measure. Pheochromocytomas are one of two types of VHL tumors that can occur before age 10. It is recommended that for children who are at risk for VHL screening should begin at an early age.

VHL has been subclassified based on the tendency to develop pheochromocytomas. Type I VHL is not associated with pheochromocytomas, whereas type II VHL predisposes to pheochromocytomas. Type IIA has a high prevalence of pheochromocytomas. For example, 57% of VHL-affected children and adults had pheochromocytomas, as seen in early studies of a type IIA large multigenerational family with mild CNS hemangioblastomas and retinal angiomas and a missense germ-line mutation in *VHL*. Type IIB, however, predisposes to pheochromocytomas along with the entire spectrum of VHL disease. Atuk *et al.* in 1998 reported a large multigenerational type IIB VHL family with pheochromocytoma having its onset between the ages of 5 and 25 years. Type IIC has been designated as familial pheochromocytoma only, without renal cell carcinoma and hemangioblastomas, in five or more reports since 1995 of kindreds with mutations in the VHL gene.

Pheochromocytomas in VHL arise from chromaffin cells, usually in the adrenal medulla. Less than 2–10% of pheochromocytomas in VHL become metastatic. In 1999, Walther and colleagues reported on 64 patients with VHL pheochromocytomas and noted that missense mutations in the VHL gene tended to be associated with extra-adrenal pheochromocytoma, younger age at presentation, and the only patient in the study with metastases.

Diagnosis

Pheochromocytomas in VHL are frequently multiple and bilateral in the adrenal medulla or may be extra-adrenal (Fig. 2). Ectopic or extra-adrenal pheochromocytomas (paragangliomas) are not uncommon and may be located in the glomus jugulare, carotid body, peri-aortic sites, spleen, kidney, and organ of Zuckerkandl (bifurcation of aorta and femoral arteries). Metastatic disease to nodes and distant organs has been seen with pheochromocytomas in VHL. CT or MRI is helpful in identifying adrenal and peri-adrenal masses, but extra-adrenal sites may require a radionuclide study called metaiodobenzylguanidine (MIBG). Patients with VHL and pheochromocytomas can have CT scans with intravenous non-ionic iodinated contrast without adverse effects. Pheochromocytomas arise from neural crest tissue and produce catecholamines that are stored in neurosecretory granules. Symptoms are variable and may include intermittent or sustained hypertension, palpitations, tachycardia, nervousness, irritability, headaches, episodic sweating, pallor, nausea, and anxiety attacks. Pheochromocytomas may cause life-threatening hypertensive crisis, myocardial infarction, cardiac failure, or metastatic disease. However, VHL-associated pheochromocytomas are often diagnosed by presymptomatic screening of family members. Walther and colleagues reported in 1999 that 35% (13 of 37) of newly diagnosed patients, detected by screening kindreds with the pheochromocytomas, had no symptoms, normal blood pressure, and normal catecholamine test results. Median tumor doubling time was 17 months.

Laboratory tests for pheochromocytoma often provide the foundation for the diagnosis. These functional tests may show activity of a pheochromocytoma when there is no adrenal or extra-adrenal tumor seen on imaging, thus prompting further studies, possibly including MIBG scintography, to locate the site of tumor activity. For many years, 24 h urinary measurements of catecholamines have been the practice in testing for functional pheochromocytoma.

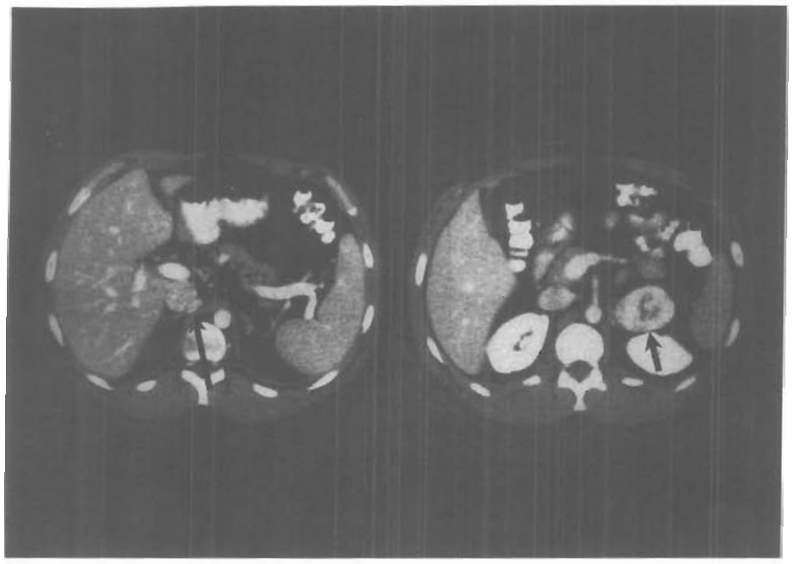

Figure 2 Bilateral pheochromocytomas in a 28-year-old male with VHL. There is a 4 cm pheochromocytoma (short arrow) on the left and a 1 cm pheochromocytoma on the right (long arrow), ectopically located behind the inferior vena cava.

A very sensitive serum test for catecholamine precursors was developed by Eisenhofer and colleagues in 1999. The sensitivity for normetanephrines and metanephrines is 97% and the specificity is 96%, whereas the sensitivities of other biochemical tests ranged from 47 to 74%. Patients with VHL had high plasma concentrations of normetanephrines; this contrasts with multiple endocrine neoplasia type 2 (MEN2) patients, who had high concentrations of metanephrine. Measurements are made of epinephrine, norepinephrine, normetanephrines, and total metanephrines. Twenty-four-hour urinary testing additionally measures dopamine and vanillylmandelic acid. It may also be necessary to perform provocative testing by glucagon stimulation and/or clonidine suppression tests to assess for functional changes that would occur under stress.

Treatment

Surgical resection is often the most common treatment for pheochromocytoma. Partial adrenalectomies and enucleations are increasingly being recommended to preserve adrenal function. Prior to surgery for pheochromocytoma, systemic treatment may be required for pharmacologic control with a combination of α- and β-adrenergic blockade. Blockade may be initiated with phenoxybenzamine, an alpha-blocker, followed by beta-blockade with propranolol or methyparatyrosine. Adrenergic blockage may be employed before, during, and even after surgery. Asymptomatic VHL pheochromocytomas found during screening before catecholamine levels are elevated are sometimes followed at intervals of 6 months to 1 year with imaging and functional tests. Walther and colleagues provided surgical decision guidelines in 1999 that include tumors with abnormal function or size greater than 3.5 cm.

Sporadic Pheochromocytomas

Brauch *et al.* in 1999 reported their study of germ-line VHL gene mutations and RET gene mutations in 62 patients with pheochromocytomas with no history of hereditary disease. They found 2 patients (3%) with VHL gene mutations and none with mutations in the RET proto-oncogene at exons 10, 11, and 13. Neumann and colleagues in 1993 reported 19.5% of unselected patients with what appeared to be sporadic pheochromocytomas, who actually had VHL as the etiology. Walther *et al.* in 1999 found pheochromocytomas in VHL to be smaller and less functional than sporadic pheochromocytomas.

Pancreatic Neuroendocrine Tumors

Solid VHL neoplasms of the pancreas are commonly nonfunctional neuroendocrine tumors. Histologically, the tumor may show a trabecular and/or glandular architecture and nests of tumor cells have been demonstrated. Pancreatic and gastrointestinal hormones

were negative by staining in the study of Libutti and colleagues reported in 1998, whereas Lubinski *et al.*, also in 1998, examined 30 tumors and found that fewer than 4 stained positive for pancreatic polypeptide, somatostatin, insulin, and/or glucagon.

A Mayo Clinic study of patients with VHL, enrolled at the clinic during a 10-year period, found neuroendocrine tumors in 17% of patients. An association with pheochromocytomas was also noted. Libutti and colleagues in 1998 studied 17 patients with surgically resected pancreatic neuroendocrine tumors and their ages ranged from 18 to 48 years.

Diagnosis

CT imaging performed pre- and post-contrast may identify a neuroendocrine tumor of the pancreas as an enhancing mass (Fig. 3). The CT is often obtained during the arterial (early) phase after contrast administration as these tumors enhance early and briefly and then become isodense with the surrounding pancreatic parenchyma. The tumors frequently occur in the pancreatic head, but are also found in the body or tail. They may be multiple and metachronous; thus, monitoring of the remaining pancreas is continued after resection of a tumor. Because these tumors are characteristically nonfunctional, detection may require periodic scanning of asymptomatic individuals at risk for VHL.

VHL neuroendocrine tumors in some series have been shown to have the potential to metastasize, most often to the liver and regional lymph nodes. Therefore, it is considered important to carefully evaluate the liver by CT and MRI in patients with VHL and PNETs.

Neuroendocrine tumors may sometimes be difficult to distinguish from multicystic cystadenomas, which are considered to be benign VHL pancreatic masses, which may also show enhancement on CT or MRI. Pancreatic neuroendocrine tumors usually enhance uniformly and intensely, whereas serous or multicystic cystadenomas are more heterogeneous and enhance to a lesser degree.

Treatment

Surgical resection is often the treatment of choice. The surgical approach is generally dictated by the location and size of the tumor. Resection may be by enucleation, pylorus-preserving pancreaticoduodenectomy (Whipple's procedure), or partial or rarely total pancreatectomy with replacement therapy. Neuroendocrine tumors of the pancreas in VHL may be slow-growing. Libutti and colleagues in 1998 found the size of the primary tumor to be correlated with the presence of metastases. Tumors less than 1 cm in size were monitored with serial scanning at intervals of 12–24 months. Management of larger tumors, 1–3 cm, depended on their location. However, preserving pancreatic functional tissue is often balanced with the known malignant potential.

Metastatic foci in the liver have been treated by therapies such as isolated hepatic perfusion with

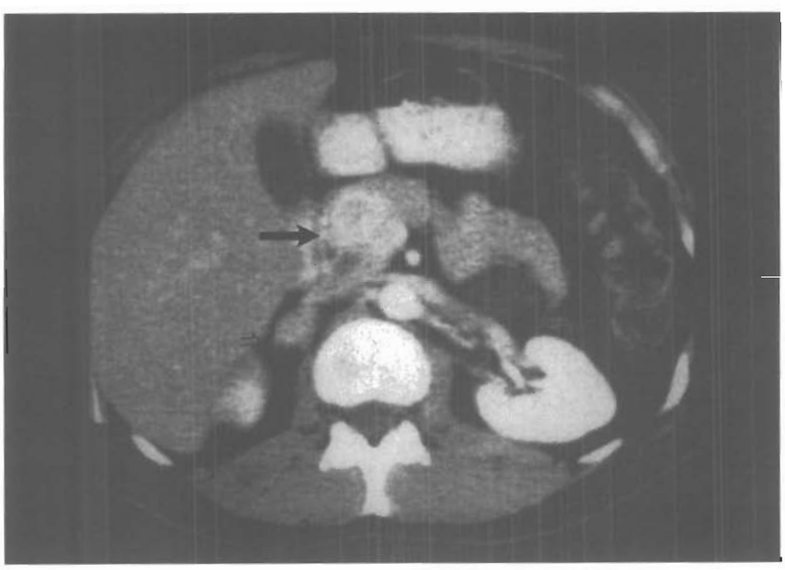

Figure 3 Pancreatic neuroendocrine tumor in a 40-year-old female with VHL. There is a large hyperenhancing mass in the pancreatic head (solid arrow) and a right pheochromocytoma (open arrow). A cyst is present in the pancreatic tail.

Melphalan, hyperthermia, radiofrequency ablation, and wedge resection.

Pancreatic Cysts and Cystadenomas

Benign cysts and cystadenomas are the most common VHL lesions in the pancreas. The frequency of individuals affected varies in different studies; frequencies ranging from 17 to 56% have been reported. Rarely, these lesions may be associated with endocrine or exocrine insufficiency. Some very large benign cysts may require treatment to relieve symptoms due to compression of the stomach outlet, intestine, or bile ducts (Fig. 4).

Hemangioblastoma of Brain and Spinal Cord

A common presenting tumor of VHL, found in 44–72% of patients, is hemangioblastoma of the CNS. This tumor is most often detected using clinical imaging. A mean age of onset of 29 years has been estimated, but affected individuals as young as 11 years and as old as 78 years with CNS hemangioblastoma have been reported.

The central nervous system is often affected by multiple tumors, each of which may have an associated cyst. Within the fixed intracranial space, growing tumors or their more rapidly expanding associated cysts impinge on normal brain structures and may cause obstructive hydrocephalus, increased intracranial pressure, and death, if they are not identified and treated.

Hemangioblastoma is a vascular tumor with histopathology demonstrating channels lined by cuboidal epithelium, nests of foamy stromal cells, and pericytes. Loss of heterozygosity of the VHL gene has been found in the stromal cell, indicating that it is the likely cell of origin of these tumors. Hemangioblastomas express excess VEGF. Berkman and colleagues demonstrated that these tumors express a large amount of VEGF. Rarely, a patient with hemangioblastoma in the CNS may have polycythemia associated with elevated erythropoietin and the erythropoietin levels decrease after removal of the tumor. Erythrocytosis or secondary polycythemia has been seen even more rarely in VHL.

Diagnosis

MRI with gadolinium demonstrates hemangioblastomas as circumscribed, brightly enhancing, spherical tumors that often arise at several sites in the cerebellum, spinal cord, intrathecal nerve roots, and brainstem. Thus, in screening evaluations, both the brain and spinal cord are imaged. Commonly, the tumors are found in the cerebellum, where they may be silent until they reach a large size. Spinal cord, brainstem, and supratentorial sites of hemangioblastomas are more problematic for treatment. Rarely, tumors occur in the temporal lobe where they may

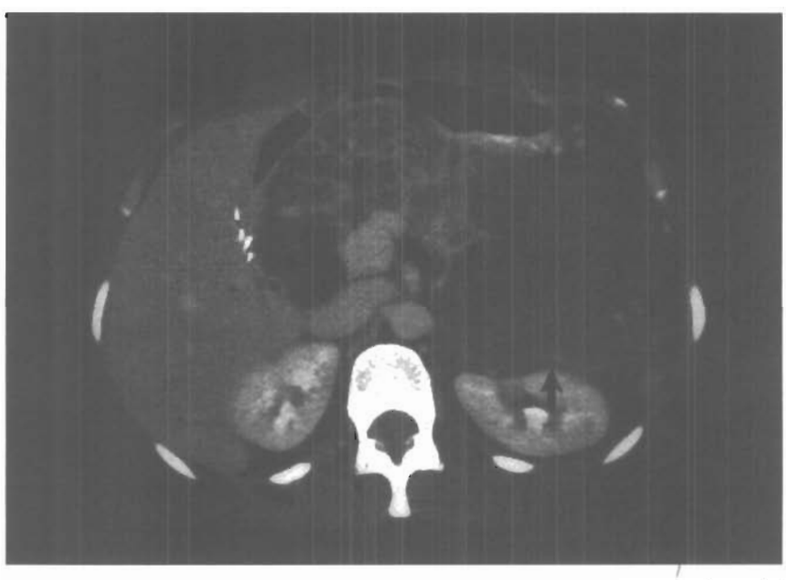

Figure 4 Severe pancreatic cystic disease. In this 34-year-old female with VHL, the pancreas is markedly enlarged by innumerable small and large pancreatic cysts including a large multilobulated cyst in the tail of the pancreas (arrow). This patient had poor gastric emptying due to extrinsic compression on the stomach.

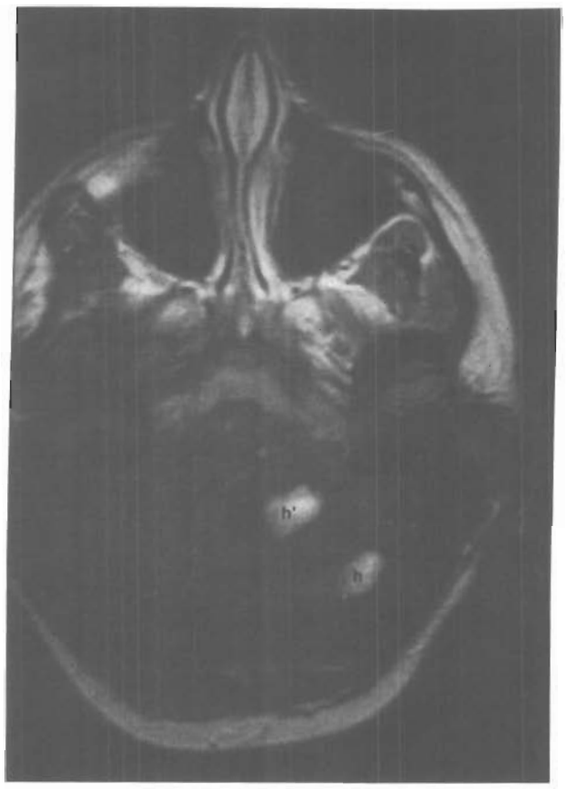

Figure 5 Multiple hemangioblastomas in a 26-year-old female with VHL. One hemangioblastoma (h) is entirely solid and the other (h')is surrounded by a cyst.

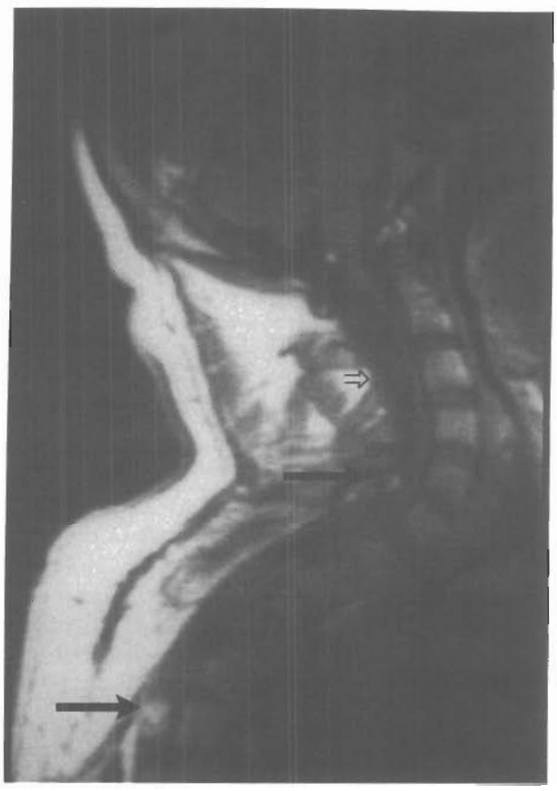

Figure 6 Multiple cervical hemangioblastomas with a syrinx. This 36-year-old male has undergone prior neurosurgical procedures to remove hemangioblastomas. A syrinx (open arrow) and several hemangioblastomas (arrows) are present.

cause seizure activity. Also rare are hemangioblastomas that arise in the tuber cinerium, near the pituitary, or in the optic nerve or chiasm, where impingement on the optic nerves or chiasm may produce loss of vision, even though the retina may be free of angiomas. When cysts are associated with the CNS tumors, they may necessitate treatment sooner because of rapidly accumulating fluid enlarging the cyst and causing pressure on normal tissue. In fact, Lindau's original description of the typical CNS lesion was a vascular mural nodule that may be difficult to locate in a large fluid-filled cyst (Fig. 5).

Spinal cord hemangioblastomas arise mainly in the cervical and thoracic regions of the spinal cord and less often in the lumbar region. In the important Melmon and Rosen report of 1964, 80% of intramedullary hemangioblastomas were accompanied by syringomyelia. These cysts in the spinal cord (Fig. 6) can cause pressure on adjacent normal tissue and symptoms such as weakness, sensory loss, urinary disturbance, and loss of balance may result. In addition to headaches, symptoms may include vertigo, nausea, vomiting, slurred speech, nystagmus, dysmetria, wide-basedgait, ataxia, and motor or sensory deficits.

Treatment

Surgical resection remains the mainstay of treatment. Because these tumors are benign and do not metastasize, neurosurgical resection is sometimes not considered until there are symptoms or signs that functional compromise may be impending. The timing of surgery is often selected to avoid neurologic deficits. In the surgical treatment of enlarging or symptomatic cysts or syrinxes, neurological surgeons often locate and remove the hemangioblastoma producing the fluid, because if the cyst is only drained and the tumor is left in place, the cyst may recur in a few days. Intraoperative color Doppler ultrasound often is used to aid the neurosurgeon in localizing small mural tumors in the cerebellum and tumors in the spinal cord.

A small fraction of cerebellar hemangioblastomas are treated with high-dose focused radiation (gamma knife surgery, linac, or other stereotactic radiosurgical ablation). In a setting of multiple tiny hemangioblastomas, on rare occasions, selected doses of conventional external-beam radiotherapy targeting the posterior fossa or spinal axis have achieved tumor control for many years.

Retinal Angiomas

Retinal angiomas (hemangioblastomas) are the commonest VHL tumor, occurring in 59% of individuals with VHL. Approximately 5% of the cases present under age 10 years, with the earliest age of onset being reported in a 1-year-old.

The histology of retinal angiomas appears to be identical to that of hemangioblastomas of the CNS and they are also considered benign. Molecular studies by Chan and colleagues in 1999 were undertaken to determine the cell of origin of hemangioblastomas. They concluded that vacuolated stromal cells represent the true neoplastic cell in retinal angiomas.

Diagnosis

Direct or indirect ophthalmoscopy may identify most retinal angiomas. Prominence of feeder vessels may be seen leading to and from some tumors. Tonometry periodically may be recommended to detect any associated glaucoma. Screening examinations are often recommended at least yearly. A pediatric ophthalmologist will often be involved in the management early in the life of individuals at risk for VHL.

Multifocal and bilateral (approximately 50%) retinal angiomas may occur. Asymptomatic lesions may be found in the periphery of the retina. However, it is not uncommon to have the tumor on the optic disc, in which case the ophthalmologist might recommend monitoring the lesion, as treatment itself could have the potential to damage the optic nerve head.

Symptoms resulting from untreated retinal angiomas may be the result of retinal detachment, capillary leak with fluid exudates, hemorrhage, macular edema, neovascularization glaucoma, and cataract. Partial or total vision loss occurs in some individuals with VHL retinal disease.

Other causes of vision loss in VHL are hemangioblastomas of the optic nerve or chiasm, increased intracranial pressure from homangioblastoma of the brain resulting in optic nerve atrophy, and postneurosurgical damage to the occipital lobe.

Treatment

Most clinicians recommend laser photocoagulation for the treatment of retinal tumors or cryotherapy for larger lesions. However, tumors on the optic disc are often monitored without treatment, which itself can be associated with damage. When tumors are diagnosed and treated early, vision loss or blindness may be prevented. Enucleation may be necessary for irreversible glaucoma with severe pain associated with ocular angiomatosis. Vitrectomy may play a role in a few cases. Further investigations are needed for the role of systemic antitumor agents. Various radiotherapy modalities have been applied on a compassionate or an experimental basis in cases of severely affected eyes not responding to the usual treatments.

Endolymphatic Sac Tumor

Manski and colleagues reported in 1997 their study of the association of an inner ear tumor with VHL. The ELST was the consensus name given for the previously diverse nomenclature of the tumor. ELSTs were detected in 13 (11%) of 121 individuals with VHL and in none of 253 patients without VHL. Hearing loss occurred at a mean age of 22 years, with the range being 12 to 50 years of age. Additional patients from the collection at the Air Force Institute of Pathology were reviewed by Manski and included a 7-year-old with ELST. Bilateral ELSTs seem to be found exclusively in patients with VHL.

The ELST is characterized by a papillary–cystic adenomatous growth, but lacks generally accepted histologic features of malignancy. However, because of its locally aggressive behavior of eroding the surrounding temporal bone, Heffner *et al.* classified it as a low-grade adenocarcinoma.

Diagnosis

Common presenting symptoms of ELST are hearing loss, tinnitus, vertigo/disequilibrium, and facial paresis. Sudden onset of complete hearing loss on the side of the tumor was found in 38% of patients with ELST. There is no clear correlation between tumor size and symptoms.

Audiologic assessment is added when there is a suspicion of a tumor. MRI of the brain may reveal a lesion, but the specific studies used for diagnosis are CT and MRI of the internal auditory canals. On CT scans, ELST is seen as an expansile and/or osteolytic lesion centered around the vestibular aqueduct in the posterior petrous bone. On MRI scans, it is characterized by heterogeneous foci of low and high

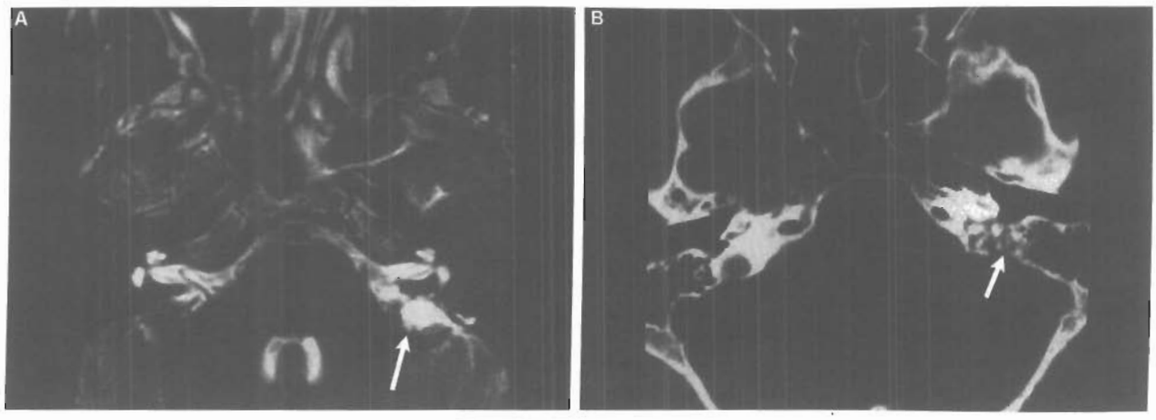

Figure 7 Endolymphatic sac tumor. This 32-year-old female with VHL developed sensorineural hearing loss on the left due to an endolymphatic sac tumor (arrow) on T2-weighted sequence MRI (A). A CT scan (B) of the same lesion demonstrates bony erosions due to the tumor (arrow).

intensities in both T1- and T2-weighted sequences (Fig. 7).

If no ELST is identified in patients with symptoms of hearing loss, tinnitus, vertigo or unexplained imbalance, repeated monitoring including audiologic and imaging studies is often advised.

Treatment

The indication and timing of surgical treatment take into consideration the slow but variable growth rate of ELSTs, preoperative hearing level, and severity of vestibular symptoms. Due to a high incidence of sudden sensorineural hearing loss associated with ELST, an early surgical intervention may be recommended for a patient with serviceable hearing as long as the tumor has not extended into the bony labyrinth. A surgical treatment may be indicated to control recalcitrant vestibular symptoms from ELST.

Surgical treatment of ELST may be curative when the tumor is completely excised via a combined retrolabyrinthine and retrosigmoid approach. Partial resection with or without radiation therapy has been reported as having a high incidence of recurrence. With complete resection, the preoperative level of hearing has been preserved in most cases and the tumor-associated vestibular symptoms can be effectively controlled.

Papillary Cystadenoma

Epididymal Papillary Cystadenomas

Choyke and colleagues in 1997 reported that 30 (54%) of 57 males with VHL had epididymal abnormalities consistent with epididymal cystadenoma, commonly 15 to 20 mm solid masses in the head of the epididymis. Onset has been seen in the teenage years. Ultrasounds of the scrotum may be used to distinguish cystadenomas of the epididymis found in males with VHL from cysts of the epididymis found in approximately one-fourth of all males (Fig. 8). The tumors are papillary cystadenomas that may be multiple and bilateral and are often identifiable on physical examination. Because these tumors are benign and most often asymptomatic, treatment is rarely required. One case of VHL with bilateral clear cell papillary cystadenoma of the epididymis that presented as infertility has been reported.

Broad Ligament Papillary Cystadenomas

In females with VHL, papillary cystadenomas of the broad ligament have been reported in rare cases, but may be unrecognized in many more cases. In 1994, Gaffey and colleagues in their report pointed out the histological similarity of papillary cystadenomas of the middle ear/temporal bone and of the female pelvic adnexa in patients with VHL. They referred to the broad ligament tumors of VHL as adnexal papillary cystadenoma of probable mesonephric origin (APMO). In 2000, Shen *et al.* reported allelic deletion of the VHL gene detected in papillary tumors of the broad ligament, thus confirming it as a VHL tumor. Reports in the literature include descriptions of women with VHL who had diagnoses of broad ligament cystadenomas between the ages of 22 and 46 years. However, in the VHL registry of the authors of this article, one patient was a teenager when she had surgery twice within a few years for resection of papillary cystadenomas of the paratubal region of the broad ligament.

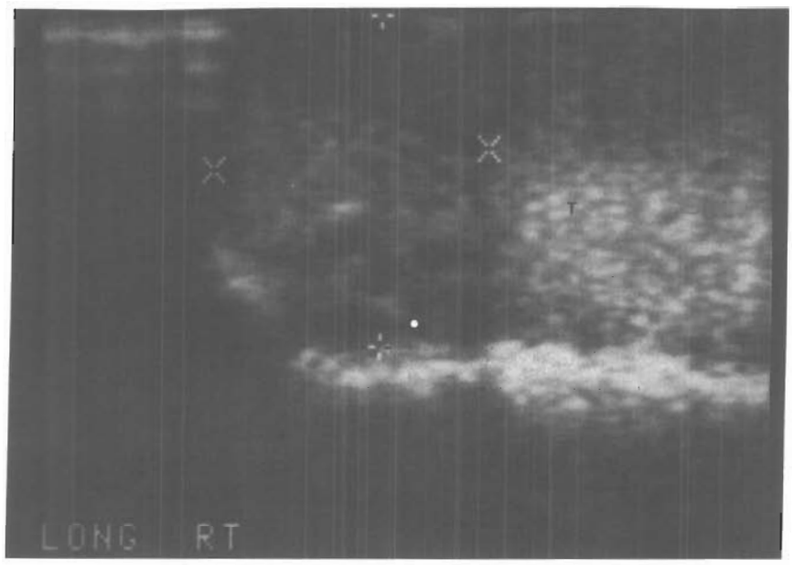

Figure 8 Cystadenoma of the epididymis. This 28-year-old male with VHL presented with a rock-like mass in the right scrotum. A longitudinal ultrasound of the scrotum reveals a normal testicle (T) and a solid mass in the head of the epididymis, which is typical of a cystadenoma of the epididymis in VHL.

FUTURE PROSPECTS

The genetics of VHL have relevance to a number of sporadic neoplasms. Of particular importance is the genetic similarity of most clear cell renal cancers. This has led to diverse molecular studies of VHL being initiated although the syndrome itself is a rare disease. Most VHL tumors have been shown to make VEGF and, as a result, VHL has become a model for the study of tumor angiogenesis and the development of anti-angiogenic agents. Investigations of the role of pVHL, elongin B/C, and Cul2 and their role with HIF in oxygen sensing may lead to therapies to restore normal function to important biochemical pathways. This may lead to the development of anti-tumor agents or modalities for use in the prevention or treatment of VHL and sporadic tumors arising due to VHL gene somatic mutations.

See Also the Following Articles

Adrenal Tumors, Molecular Pathogenesis • Hypertension, Endocrine • Pheochromocytoma

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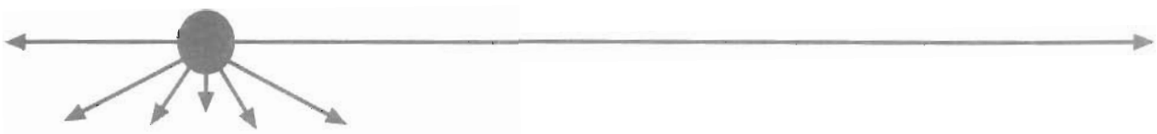

von Recklinghausen's Disease

see Neurofibromatosis